Screening and Identification of Multitargeted Lead Compounds in Parkinson's Disease by Computational Techniques

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Introduction:

Parkinson's disease (PD) has become the second most prevalent neurodegenerative disease in the world [1]. The history of Parkinson's disease is closely correlated with therapeutic interventions. These interventions might range from chance observation to carefully monitored clinical trials of specially formulated drugs [2].

Approximately 2% of the population over 60 years old are currently affected. Bradykinesia, stiffness, and rest tremor are the main motoric disorders caused by striatal dopamine insufficiency, which is caused by the loss of dopaminergic cells in the substantia nigra. Debilitating non-motor symptoms, such as autonomic dysregulation, can develop in the early or late stages of the disease[3,4] . In addition to neuropsychiatric symptoms (such as depression, cognitive impairment, dementia, and psychosis), sensory abnormalities, and gastrointestinal dysfunctions, sleep problems are one of the most prevalent non-motor consequences of Parkinson's disease [5].

Gaucher's disease, a recessive ailment brought on by mutations in the gene glucocerebrosidase (GBA), which codes for the lysosomal enzyme glucocerebrosidase, can occasionally have Parkinson's-like symptoms rigidity, postrural instability, resting tremor, bradykinesia, and gait impairment are the five hallmarks of Parkinson's disease [3,6].Levodopa, Ropinirole, Entacapone, Selegiline, and Benzatropine are recent drugs that can be used to treat PD [7].

Levodopa-by slowing down bodily movements—helps to lessen excessive trembling. It functions by raising dopamine levels, a chemical messenger required to control aberrant movements. Dopamine, a chemical messenger required to control aberrant movements, is made more abundant when ropinirole is taken. Levodopa and Entacapone both have similar effects. Selegiline functions by raising the brain's dopamine levels. They block MAO-B.To treat Parkinson's disease symptoms like stiffness or tremors, benzatropine is taken in combination with other medications.

The main adverse effects of the aforementioned medications are nausea, weakness, dizziness, and vomiting, among others.

Natural products are excellent sources of bioactive compounds that can be used to explore new therapeutic potential in the PD pathogenesis [8], such as plants, animals and marine are natural products. Plants contain bioactive substances such coenzyme Q, carnitine,

flavonoids, and carotenoids. Altered alpha synuclein aggregation, MAO-B, neurotropic factors, and reactive oxygen species (ROS) are among the therapeutic targets for PD [9].

The aberrant aggregation of alpha synuclein has received extensive research as a primary treatment target for Parkinson's disease (PD) since it is linked to neurotoxicity in the brain and causes a progressive loss of DA neurons as the disease progresses. The mitochondria's outer membrane is where MAO-B is primarily found.

Dopamine neurotransmitters are specifically metabolized by MAO-B, which also generates ROS that directly harm DA neurons. By preventing dopamine's breakdown, MAO-B inhibitors could increase synaptic dopamine levels and eventually have neuroprotective benefits [9].

Selegiline and rasagiline are the two MAO-B inhibitors that are currently approved by the US FDA for the treatment of Parkinson's disease. MAO-B inhibitors are safe, have few major side effects, and alleviate the motor symptoms of PD in a small but meaningful way[4].Inhibiting MAO-B is a key goal in the hunt for novel PD medications [7]

Several genes have so far been found to be responsible for various forms of Parkinson's disease. **SNCA**-The first causal PD gene, SNCA, was discovered in a large Italian family segregating a pathogenic missense variant, p.Ala53Thr. The natively unfolded, soluble 144 aa SNCA protein is normally located in the cytoplasm or linked to lipid membranes. It is encoded by the three distinct SNCA transcripts. The biological function of SNCA in the presynaptic terminal's vesicle turnover and neurotransmitter release. **LRRK2**-The second causative gene connected to autosomal dominant hereditary PD is the leucine rich repeat kinase 2 gene (LRRK2). Its 51 exons, which code for the LRRK2 protein, are found in the transcript. Codon Arg1441 has 80 missense mutations that change it. **PARK2**-Parkin is encoded by PARK2, which is 1.38 Mb in size. The initial mutation studies showed that PARK2 had a wide range of loss-of-function mutations, including straightforward changes like nonsense, missense, and splice site mutations. Parkin proteins serve as targets for protein degradation and the upkeep of mitochondrial function in their normal functions.

PINK1-The putative Serine/Threonine kinase PINK1 protein participates in the mitochondrial response to cellular and oxidative stress. In the purported PINK1/Parkin pathway, PINK1 is a key actor who controls the morphology and functionality of the mitochondria in response to stimuli. There are nonsense and missense mutations on the PINK1 mutation spectrum. **PARK7 or DJ-1**-DJ-1 protein was discovered to be H2O2 sensitive,

indicating that DJ-1 serves as an antioxidant and a sensor for oxidative stress, such as dopamine poisoning. Similar to homozygous carriers of the recessive PARK2 and PINK1 genes, homozygous mutations in the recessive PARK7 gene [10].

Structure-based drug design (SBDD) has many uses, including computer-aided drug design, which is crucial for finding new treatments for the chosen therapeutic targets [11]

Selected protein Targets in PD

Gene Name	Protein Name	PDB ID
SNCA	Alpha Synuclein	8A9L
LRRK2	LRRK2	7LHT
PARK2	Parkin	4K95
PINK1	PINK1	5TR5
PARK7 or DJ-1	DJ-1	3BWE

Literature Review

Theodora Ntetsika et. al. (2021) report that current treatments for Parkinson's disease focus on improving quality of life and life expectancy but do not halt or reverse disease progression. Exploring potential PD treatments can serve as targets of therapeutic interventions aiming to slow or modify disease progression.

According Catherine et. al. (2021) reported has no disease-modifying medication at the moment, in part because Parkinson's disease therapeutic targets were not properly identified and validated. Researchers examine over 3,000 genes that encode drug-resistant proteins and forecast their effectiveness as treatment targets for Parkinson's disease using mendelian randomization. In order to simulate drug exposure, expression and protein quantitative trait loci are used. The causal impact on Parkinson's disease risk, age at onset, and progression is then examined.

Khan et.al. (2021) investigated the potent Levodopa, plant like mucuna pruriens L.-is a annual legume, 5% levodopa present.levodopa is a phenolic Phyto compound. Alizarin is a hydroxyl Anthtraquinone compound isolated from plant Rubia cordifolia, posses some anti PD properties.atropine and hyoscyamine extracted from the leaves of Hyoscyamus niger, use for inhibition of MAO enzyme in mice PD.

According chunhui et. al. (2019) natural medicines for the treatment of Parkinson's disease that are derived from the sea.Natural chemicals derived from marine sources have the potential to have a wide range of pharmacological effects and could be very helpful in the creation of novel drugs. Mannosyl glycerate (MG), Piloquinone B, Neochinulin A, Xyloketal B, 3-methy-orsellinic acid, astaxanthin, and other marine natural products. These marine-based natural products have activity at the PD target location.

Reportedly, Md Solayman et.al. (2017) stated that anti-Parkinson drugs such as levodopa, carbidopa, dopamine (DA) agonists, monoamine oxidase type B inhibitors, and anticholinergics to replace DA to treat PD. In fact, for many years natural products from plants, fruits, and vegetables have shown promise as anti-Parkinson agents.

Jacobus P. Petzer and Anel Petzer (2015) demonstrated that caffeine is a well-known adenosine receptor antagonist, and has been recently considered as a lead compound for the design and discovery of A2A antagonists and MAO-B inhibitors

Jayaraj et.al. (2013) reported, plant-derived chemicals, including (a) stimovul (b) 7,8-dihydroxycoumarin, (c) etorphine (d) propoxyphene, and (e) pentazdine, were used for in silico

molecular docking against -synuclein. Using Accelrys Discovery Studio 3.5, these compounds' Lipinski and ADMET characteristics were examined. Lead IT was used to perform molecular docking between the ligand and protein. Results showed that Stimovul, with a docking score of -4.5122, was the best-fitting ligand against the active region of -synuclein, and that SER 87 and VAL 95, along with other chemicals, were the interacting amino acids.

According to Christopher et.al. (2011) early writings contain elements that may be related to Parkinson's disease; James Parkinson wrote the first concise medical description in 1817. Separated Parkinson's disease from other tremor-causing disorders such as multiple sclerosis, and identified cases that would later likely be categorized as Parkinsonism-plus syndromes. Anticholinergic medications have been used to treat Parkinson's disease since the nineteenth century, when early treatments were based on empirical observation.

According to Thomas et.al. (2007), reported on pathogenic mutations in Parkinson's disease, genetic loci are identified for Parkinson's disease such as PARK1 (alpha synuclein), PARK2(parkin), LRRK2, PINK1 and many others. In genetic causes of PD only five gene product linked to monogenic forms of PD like PARK1, PARK2, PARK6, PARK7, and PARK8.genes associated with PD also link damage of oxidative in disease pathogenesis and Mitochondria. These include alpha Synuclein, parkin, DJ-1, PINK1 AND LRRK2.

According to s. ekins et. al. (2007), In Vitro data production & in silico procedures are typically employed to build and evaluate the model. But during the past ten years, we have seen an increase in the use of computational (in silico) methodologies to pharmacology's creation and testing of hypothesis. A rapidly expanding field, in silico pharmacology. Deals with creation of methods for employing software to gather, examine and combine biological and medical data from a wide range of sources. helpful to save time and cost required for new drug development and discovery.

Objectives

1. To Screen the bioactive compounds from natural origin.
2. To identify the drug targets in PD.
3. To predict the molecular descriptors properties of Bioactive compounds.
4. To predict the ADMET properties of selected Bioactive compounds.
5. To calculate the binding free energy of docked conformers.

Methodology

1. Data collection: To compile information on the bioactive substances found in plants, animals, fungi, and other naturally occurring substances. Established databases, academic literature, and materials on conventional medicine can all be excellent sources of knowledge.

2. Compound Selection: Choose a variety of bioactive substances according to their known therapeutic effects, ethnopharmacological expertise, and applicability to Parkinson's disease. As these are frequently linked to potential therapeutic effects against PD, take into account substances with anti-inflammatory, antioxidant, neuroprotective, and cholinesterase inhibitory actions.

3. Database Search: To find bioactive substances from natural sources, use a variety of databases and online tools. Databases for herbal medicines, animal natural products, PubChem, and ChEMBL are a few examples.

4. Pharmacophore Modelling: To create pharmacophore models utilizing computational methods to discover properties that are shared by numerous recognized bioactive substances. With the help of these models, natural substance databases can be virtually screened to identify candidate compounds that match the specified pharmacophoric properties.

5.The ADME filtering process and molecular descriptors: Calculate molecular descriptors including molecular weight, hydrogen bond donors/acceptors, lipophilicity (logP), and other physicochemical parameters using computational methods. To prioritize substances with favorable pharmacokinetic profiles, use filters based on drug-likeness standards and absorption, distribution, metabolism, and excretion (ADME) characteristics[13].

6. Virtual Screening: To assess the binding affinity and interactions of the chosen bioactive compounds against important Parkinson's disease targets such alpha synuclein aggregation, MAO-B, neurotrophic factors, reactive oxygen species, use docking simulations or ligand-based virtual screening approaches. Prioritize substances according to their expected binding affinities using ligand-based techniques such as molecular fingerprints or shape-based similarities, or molecular docking tools such as AutoDock or Vina.

7. Validation and Experimental Studies: To create a shortlist of the best bioactive compounds from the virtual screening and conduct experimental research to confirm the compounds' efficacy against the targets of Parkinson's disease.

Molecular Docking Tools

Dock-Developed by Cambridge Crystallographic Data Center(CCDC).

GOLD-Developed by University of California , San Franciso

GRAMM-Global Range Molecular Matching

Protein Docking-A Center for Bioinformatics, University of Kansas.

Glide-Schrodinger LLC.

SANJEEVINI- Developed by IIT Delhi

FlexX- T.Lengauer and Rarey

Autodock-Developed by Moris and co- workers, The Scripps Research Institute.

Importance of study

The effectiveness of bioactive chemicals acquired from various natural sources must be confirmed. It becomes identified for the population in developing and under developing countries to enrich their health associated with Parkinson's disease. It becomes good therapeutic agent to reduce the rate of mortality and morbidity.

Work plan

YEAR	TARGETS TO BE ACHIEVED
1ST	Review of literature of Parkinson's disease, its stages of development and mechanism. Screening bioactive compounds in natural resources like plants, animals, and others Analysis of bioactive compounds with CADD tools
2nd	Virtual screening of bioactive compounds
3rd	Annotation and analysis of data, submission of final thesis

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